THE USE OF A SCREENING BLOOD SUGAR TEST TO INCREASE THE IDENTIFICATION OF GESTATIONAL DIABETES

by

Lynn Rogalla Dixon

A thesis submitted to the faculty of The
University of Utah in partial fulfillment of the requirements
for the degree of

Master of Science

College of Nursing

The University of Utah

August, 1980

THE UNIVERSITY OF UTAH GRADUATE SCHOOL

SUPERVISORY COMMITTEE APPROVAL

of a thesis submitted by

Lynn Rogalla Dixon

I have read this thesis and have found it to be of satisfactory quality for a master's degree.

Date

Lorraine Sevcovic, C.N.M., M.S.
Chairman, Supervisory Committee

I have read this thesis and have found it to be of satisfactory quality for a master's

Date

Mary Anne Lapin Graf,
Member, Supervisory Committee

I have read this thesis and have found it to be of satisfactory quality for a master's degree.

Date

Howard S. Berk, M.D.
Member, Supervisory Committee

THE UNIVERSITY OF UTAH GRADUATE SCHOOL

FINAL READING APPROVAL

To the Graduate Council of The University of Utah:

I have read the thesis of [redacted] Dixon [redacted] in its final form and have found that (1) its format, citations, and bibliographic style are consistent and acceptable; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Graduate School.

[redacted]

Date

[redacted]

Approved for the Major Department

[redacted]

Linda K. Amos, Ed.D., F.A.A.N.
Chairman/ Dean

Approved for the Graduate Council

[redacted]

ABSTRACT

Abnormal carbohydrate metabolism frequently first appears in women during pregnancy as a transient condition. This form of latent diabetes mellitus is termed gestational diabetes. Diabetes in pregnancy, either overt or gestational, poses an increased risk to both mother and fetus. Fortunately, such risks have been greatly reduced by advances in the treatment of this complication. Obviously, the implementation and the effectiveness of special antenatal care is dependent on an accurate and early diagnosis. However, the identification of gestational diabetics is inherently difficult because these women frequently lack the clinical symptoms and signs associated with overt diabetes mellitus.

The purpose of this study was to examine the effectiveness of a one-hour blood sugar test as a method to detect gestational diabetes, and to compare its effectiveness to that of the more commonly used screening criteria - family history of diabetes, previous large infant, previous poor obstetrical history, and maternal obesity. In addition, maternal age and parity was examined to determine their usefulness in predicting the development of gestational diabetes. This retrospective study was based on an examination of the medical records of 630 women, 531 of whom were administered a one-hour blood sugar test in addition to being screened for gestational diabetes by traditional methods. Seven gestational diabetics were identified through the use of a

one-hour glucose screening test, and five of these seven prenatal patients also had traditional screening factors present. The remaining two patients representing 29 percent of the gestational diabetics were identified solely by the one-hour test. A maternal age of 25 years or more was the only other factor which demonstrated a significant association with gestational diabetes. Macrosomia, which was not correlated with gestational diabetes, was however significantly associated with maternal obesity, maternal weight gain of greater than 30 pounds during the pregnancy, maternal age of 25 years or more, and a past history of large infants.

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGMENTS

I would like to thank Donna Thorne, Nelda Peterson, Randy Austen, and Kay Schultz and the staffs of the medical records departments of the Family Health Program Centers of Utah for their help. Without it, this study would not have been possible.

My very special thanks to my husband John for all his advice, criticism, typing, love and encouragement, and to our daughter Sarah for bringing so much joy into our lives this year. And to my mother, Lucille Rogalla, and my aunt, Stella Draszkiewicz, for their constant support and for their very special help when I needed it most, I thank you.

I would also like to thank the members of my committee, Lorraine Sevcovic, Mary Anne Graf, and Howard Berk, for their guidance.

CHAPTER I

INTRODUCTION

Diabetogenic Nature of Normal Pregnancy and Its Relationship to Gestational Diabetes

Several factors in normal pregnancy are know to cause physiological alterations in carbohydrate metabolism, some of which are diabetogenic in nature. Two phenomena are particularly important. First, the fetus is an obligate glucose consumer (Adam, 1971) and continually withdraws glucose, amino acids, and fatty acids (but not insulin) from the mother's circulation in order to fuel its own growth and development. Glucose demand by the fetus tends to increase during pregnancy. This is reflected in the fact that the maternal glucose uptake at term has increased from a nonpregnant rate of 2 to 3 mg./kg./min. to 6 mg./kg./min. (Felig, 1977). Second, placental contrainsulin factors increase throughout pregnancy. These factors increase maternal resistance to insulin (Freinkel, Metzger, Nitzan, Hare, Shambaugh, Marshall, Surmacznska, & Nagel, 1972; Trayner, Welborn, Rubenstein, Fraser, 1967) and result in decreased peripheral utilization of glucose (Burt, 1960) and hyperlipidemia (Freinkel, 1964). These factors include estrogen (Javier, Gershberg, & Hulse, 1968; Frantz & Rabkin, 1965), human growth hormone (Catt, 1970), placental lactogen (Spellacy & Cohn, 1973) and

two sets of insulin degrading enzymes of placental origin (Posner, 1973).

By the 24th to 28th week of gestation, a net antagonism to the action of circulating insulin results in a maternal pancreatic response of increased insulin secretion. This has been demonstrated by radioimmunossay for insulin and is most marked in the third trimester (Spellacy & Goetz, 1963). Hypertrophy and hyperplasia of the pancreas during pregnancy, primarily involving the insulin-producing beta cells, anatomically confirms this response (Felig, 1977).

Pregnancy can thus be viewed as a unique biological test of the functional reserve of a woman's beta-cells. Frienkel et al. (1972) suggested that gestational diabetes, a form of latent diabetes mellitus which appears during pregnancy, develops because these cells are unable to maintain the increased insulin production which is demanded during pregnancy in order to maintain gestational glucose homeostasis. Yen, Tsai, and Vela (1971) demonstrated that the development of hyperglycemia and the retardation of glucose disposition (K-value) in gestational diabetics were clearly related to delayed insulin release as well as to a defect in the quantity and quality of insulin secreted in response to an intravenous glucose tolerance test (IVGTT). At six to eight weeks postpartum, when the diabetogenic influence of pregnancy was absent, they found that the inadequate initial insulin response persisted, but that glucose disposition had returned to the normal range.

Complications Associated with Gestational Diabetes

The perinatal and maternal risks associated with overt diabetes mellitus in pregnancy are well known. They include increased fetal wastage, perinatal mortality, preeclampsia, polyhydramnios, maternal diabetic instability, fetal malformations, large babies, neonatal respiratory distress, hypoglycemia, and prematurity. It is generally agreed that gestational diabetics have a greater tendency to suffer these complications than does the general population (Abell & Beischer, 1974).

Increased fetal wastage has been shown to be significantly higher in women with abnormal glucose tolerance tests (Notelovitz, 1970; O'Sullivan, 1970; O'Sullivan, Gellis, & Tenney, 1966). Also, investigators have reported perinatal losses of 20 to 50 percent during periods ranging from 5 to 12 years prior to a diagnosis of overt diabetes (Dandrow & O'Sullivan, 1966; Jackson, 1952; Moss & Mulholland, 1951; Pedowitz & Shlevin, 1957).

Infants of gestational diabetics do show a higher rate of perinatal morbidity, particularly respiratory distress and hypoglycemia (Hadden & Harley, 1967; Haworth & Dilling, 1975; Velasco, Benjamin, & Gordon, 1966; Willenger, 1966). Pildes (1973) states that 10 to 20 percent of these infants suffer complications during the neonatal period. In a study examining the relationship between maternal glucose intolerance and neonatal blood glucose, Haworth and Dilling (1976) found hypoglycemia in 77 percent of infants of diabetic mothers compared to only 8 percent of infants of mothers

with minor degrees of glucose intolerance. There was no control group of mothers who had normal glucose tolerances. He also noted that the best predictor of neonatal hypoglycemia was the blood glucose level at two hours during an oral glucose tolerance test.

Pehrson (1974), in an extensive review of the literature, cited many studies which have shown a higher than normal frequency of macrosomia among infants of diabetic mothers. However, several other factors, seemingly unrelated to diabetes, are also associated with macrosomia. These include a genetic predisposition, increasing parity (McKeown & Gibson, 1951), obesity of the mother (O'Sullivan et al., 1966), and previous large babies (Stallone & Ziel, 1974). Farquhar (1971) pointed out that variations in the birth weights of siblings born to prediabetic females may well be due to cyclic exacerbations and remissions characteristic of this stage of the disease. Macrosomia is, of course, associated with a number of negative obstetrical sequelae including birth traumas to mother and infant, fetal malpresentation, dystocia, and cephalopelvic disproportion.

It is not clear how serious is the risk of prematurity for infants of gestational diabetics. The rate of prematurity for infants born to prediabetic mothers varies from 4 percent to about 17 percent for the various populations for which this statistic has been reported (Moss et al., 1951; Paton 1948; Reis, de Costa, & Allweiss, 1950). However, in judging the significance of these figures, one must bear in mind that 5 to 10 percent of <u>all</u> live births are premature (Greenhill & Friedman, 1974, p. 697).

The frequency of congenital malformations among infants of overt diabetic mothers appears to be higher than among those of nondiabetic mothers. Amankwah, Prentice, and Fleury (1977) found that 13.6 percent of babies born to 44 known gestational diabetics had congenital abnormalities. Wilkerson and O'Sullivan (1963) reported that the incidence of congenital malformations in the population of diabetics they studied was 7 percent for the combined Class A through Class C diabetics (White's Classification). They also found that the incidence of these malformations was directly proportional to the degree of control of the disease. For prediabetics, that is for women who have not yet demonstrated any abnormal glucose metabolism, the frequency of congenital malformations reported in the literature varies from 4 to 9 percent (Carrington, 1960; Hagbard & Svanborg, 1960). On the other hand, Koller (1953) and Haworth and Dilling (1975) found no higher incidence of malformations among babies born to women with gestational diabetes than among those born to women in their general populations. Some of the strongest evidence of a link between diabetes and malformations comes from a study conducted by Navarete, Rojas, Alger, and Paniagua (1970). They examined a group of 349 women who have previously delivered a malformed child and a control group of 100 women of similar age and parity. The first group was divided into three subgroups: I. Women who had delivered a malformed child less than one year earlier; II. Women who had had a congenitally malformed child 1-12 years earlier; and III. Women delivered of a malformed child 13-25 years previously. The control group was similarly subdivided

according to time since their first pregnancy. The investigators observed a high frequency of known diabetes among the women who had previously delivered a malformed child: 6.6%, 14.8%, and 34.3% in Groups I, II, and III, respectively. The total incidence of diabetes (known diabetics plus women with an abnormal glucose tolerance) was even higher in the three groups: 16.7%, 40.4%, and 53.1%, respectively. In the control group, only one known diabetic and three women with abnormal glucose tolerance tests were discovered.

Dandrow and O'Sullivan (1966) reported a trend towards higher risk of preeclampsia and polyhydramnios among gestational diabetics. Unfortunately, their sample size was too small for statistical analysis. Among prediabetics, Moss and Mulholland (1951) found 14.2 percent to have preeclampsia. Lunnell (1966) also reported a relationship between preeclampsia and eclampsia, and decreased glucose tolerance, but it was not statistically significant after other complications of pregnancy were factored out.

Apart from increasing the risks involved in a current pregnancy, gestational diabetes increases the likelihood that a woman will later develop the permanent, overt form of the disease. In three followup studies of 5, 10, and 12 years duration, it was found that the percentages of gestational diabetics who later developed overt diabetes were 20, 30, and 60, respectively (Michal, Begneaud, & Weese, 1966; Notelovitz, 1970; O'Sullivan & Mahan, 1964).

Another long-term complication of diabetes during pregnancy affects

the child. In a followup study, Churchill, Berendes, and Nemore (1969) found that infants of mothers whose diabetes was uncontrolled or left untreated to the point of developing both acetonuria and hyperglycemia had significantly lower I.Q.'s than their peers at four years of age. Stehbens, Baker, and Kitchell (1977) reached similar conclusions from the results of their five year study.

Fortunately, rigorous screening and improved medical management have brought about a steady reduction in mortality and morbidity rates and in the rate of congenital malformations associated with gestational diabetes (Adashi, Pinto, & Tyson, 1979; Pedersen, Molsted-Pedersen, & Anderson, 1974). Among the management modalities used for gestational diabetics are diet, use of insulin as indicated, use of urinary estriols, amniocentesis, and, according to some authorities, elective delivery at or before 38 weeks (Bates, 1974; Drury, 1970; O'Sullivan, Mahan, Charles, & Dandrow, 1974). In particular, the maintenance of plasma glucose concentrations no greater than 100 mg/100 ml throughout the pregnancy has been claimed by several investigators to reduce the risk to mother and child to a negligible level regardless of the severity of the disease (Gyves, Rodman, Little, Fanaroff, & Merkatz, 1977; Karlsson & Kjellmer, 1972; Tyson & Hock, 1976). This has also resulted in a reduction in the number of Caesarean sections (Abell & Beischer, 1974). This is apparently due, at least in part, to a reduction in the incidence of fetal macrosomia (Coustan & Lewis, 1978; Gyves et al., 1977). In fact, routine preterm delivery, with all its associated risks, is

no longer considered by some physicians to be justified for well-managed gestational diabetics (Khojandi, Tsai, & Tyson, 1974; Stallone & Ziel, 1974). The importance of improved screening for glucose tolerance is readily apparent - only those gestational diabetics which are identified can benefit from progressive medical management.

Diagnosis of Diabetes Mellitus in Pregnancy

Estimation of blood sugar remains the sole criteria for early clinical identification of the diabetic state. This is generally accomplished by the administration of a three hour oral glucose tolerance test (OGTT). If two or more abnormal values are obtained, the diagnosis is made. Blood sugar studies following a glucose load have not, however, shown any clear-cut demarcation between pregnant nondiabetic and pregnant diabetic populations (Alford, Martin, & Pearson, 1971; O'Sullivan & Mahan, 1964). Thus, any diagnostic definition of gestational diabetes is somewhat arbitrary at its lower level of detection.

It is known that pregnancy and the immediate puerperium significantly alter "normal" nonpregnant blood sugar values. In a random group of 163 pregnant women, in which known diabetics were excluded, a three hour OGTT was administered periodically during their pregnancy and three to six weeks postpartum (O'Sullivan, 1970). The blood sugar values for the pregnant population, compared to those of a matched nonpregnant sample, revealed lower fasting values and elevated postglucose values at one, two, or three

hours. These findings demonstrate the need to establish OGTT values which would separate alterations in glucose tolerance normally associated with pregnancy from those associated with the development of diabetes in pregnancy. O'Sullivan (1970) then tested 752 sequentially registering prenatal patients with a three hour OGTT and followed them for up to 12 years to see who developed the disease. He defined four classes of OGTT results: 1) Negative Blood Glucose (levels up to one standard deviation above the mean); 2) Test Level I (glucose levels between one and two standard deviations above the mean); 3) Test Level II (glucose levels between two and three standard deviations above the mean); and 4) Test Level III (glucose levels greater than three standard deviations above the mean. Of the 164 patients who later developed diabetes, 0.7% had tested negative, 13.3% were in Level I, 29.1% in Level II, and 52.8% were in Level III. O'Sullivan concluded that specific blood glucose levels in pregnancy were clearly related to later development of diabetes and proposed the use of Test Level II (with values rounded to the nearest 0.5) for the diagnosis of gestational diabetes. Test Level II was chosen as the diagnostic cut-off in order to minimize the economic problems associated with long-term care and the psychological ill effects to the many patients in Test Level I who would not develop diabetes. The blood sugar levels O'Sullivan has proposed as diagnostic of gestational diabetes have received wide acceptance (Abell & Beischer, 1974; Gyves et al., 1977; Khojandi et al., 1974) and are used in this study.

Several other points concerning oral glucose tolerance tests during

pregnancy are pertinent. O'Sullivan (1970) contrasted the minimum values he recommends to be used to diagnose diabetes in pregnancy and nonpregnant patients employing three hour OGTT. They are as follows:

	Nonpregnant	Pregnant
Fasting value	100 mg/100 ml	90 mg/100 ml
One-hour value	170-160 mg/100 ml	165 mg/100 ml
Two-hour value	120 mg/100 ml	145 mg/100 ml
Three-hour value	110 mg/100 ml	125 mg/100 ml

The above glucose values are for whole blood. When plasma is used, they should be increased by 14 percent (O'Sullivan & Kantor, 1963). Other factors which will increase the glucose value are hemolysis, low hematocrit, and high plasma protein concentration.

There is no concensus concerning the optimal level of the glucose challenge - both 50 gm and 100 gm challenges are used. Some physicians place patients on a high carbohydrate diet for three days prior to the test, while others prefer patients to continue to eat normally. Wilkerson (1960) has shown that significant variations in carbohydrate intake above the minimum of 50 gm per day had very little effect on OGTT results. Several investigators have demonstrated that the two-hour blood sugar value is the most predictive of an abnormal tolerance. Tests are evaluated in terms of sensitivity and specificity. "Sensitivity" is the percent of patients correctly identified by a test; "specificity" is the percent who are correctly excluded. Wilkerson and O'Sullivan (1963) found the sensitivity of the two-hour value to be 95.8 percent

and its specificity to be 94.6 percent. Both Notelovitz (1970) and Hohe (1971) recommend using a two-hour GTT in preference to the full three-hour test since they found the two results almost identical and the two-hour test is more economical of both time and money. It should be noted here that the degree of abnormality in an OGTT at the time of diagnosis is not predictive of the pregnancy's outcome. Rather, the duration and the degree of metabolic derangement are the primary influences on fetal outcome. Obviously the earlier the diagnosis and commencement of treatment, the better the fetal outcome that can be expected. Therefore, it is recommended that women who seem likely to develop gestational diabetes (for example, those with a previous history of the disease) should be screened on the first prenatal visit. If the tests are negative, they should be repeated after the 28th week, which is when the diabetogenic effects of pregnancy begin to manifest themselves (Gyves et al., 1977; Khojandi et al., 1974). Tyson et al. (1976) found that 80 percent of women retested had a positive OGTT later in their pregnancy. Drury (1970) pointed out that negative tests before the 36th week cannot rule out the diagnosis of gestational diabetes since the impairment of glucose tolerance is progressive with pregnancy.

Finally, it may be pointed out that several investigators advocate an intravenous rather than an oral GTT for screening and diagnosing abnormal glucose tolerance (Baker & Hutchinson, 1968; Pehrson, 1974; Silverstone, Solomons, & Rubricius, 1963). Unfortunately, the OGTT and IVGTT frequently give disparate results in the same individual (Garnet, Helsel, &

Piver, 1968; Ocampo, Coserin, & Quilligan, 1964; Singh & Arshat, 1978). The advocates of IVGTT object to the OGTT because changes in gastrointestinal motility during pregnancy are known to interfere with the absorption of glucose. Since the IVGTT bypasses the gastrointestinal tract, it is claimed to more accurately test the insulin response of the pancreas to the glucose challenge. Garnet et al. (1968) claimed that the IVGTT is a more accurate means to identify milder forms of abnormal glucose metabolism. However, the evidence from their study does not support this assertion. In a six year prospective study, Hadden, Harley, Kajtar, and Montgomery (1971) compared the value of several tests in predicting fetal outcome. They compared a two-hour OGTT, a Cortisone GTT, and an IVGTT, each administered at 32 weeks gestation. There was no clear difference among the tests. Benjamin and Casper (1967) conducted a study in which 144 patients were given both an OGTT and an IVGTT in the third trimester of pregnancy and again between six weeks and three months after delivery. They claim that the oral test is more specific. Their main objection to the IVGTT is that it produced a much higher rate of false negatives (47%) than did the OGTT (12%). However, these authors did note that the true relative and absolute reliability of these tests can only be determined by long-term prospective studies. No such studies were found in the literature.

Controversy Regarding Screening Methods for Gestational Diabetes

A complete glucose tolerance test for every patient several times

during pregnancy is the only means of detecting all gestational diabetics (MacAffee & Beischer, 1974) and has been recommended by some for all pregnant patients. However, the detection rate in a given population may not justify the laboratory and staffing costs involved. An incidence of only 0.7 percent was found in an Australian population in which 2,000 consecutive patients received a three-hour OGTT (Abell & Beischer, 1975). Thus, there is a need to establish a method of screening which would identify most pregnant women at risk of abnormal glucose tolerance without requiring a complete three-hour OGTT for all patients.

The traditional method of screening for gestational diabetes has been to determine first the presence of certain clinical criteria (MacAffee et al., 1974; Moss et al., 1949). If one or more are present, a three-hour OGTT is then ordered. These "classical" criteria include: 1) family history of diabetes (sometimes limited to a first degree relative); 2) birth of a large baby (variously defined as greater than or equal to nine or to ten pounds); 3) poor past obstetrical history (which includes two or more unexplained abortions, stillbirths, or neonatal deaths; premature birth, congenital malformations, history of proteinuria, hypertension, polyhydramnios, and excessive weight gain); 4) maternal obesity (usually defined as a prepregnant weight 20% or more over the ideal); and 5) glycosuria (occasionally limited to the second fasting urine specimen or a level greater than 1+ on two or more occasions). O'Sullivan (1961) screened 20,070 registered prenatal patients using these criteria alone and identified one gestational diabetic out of every 116 patients

- 0.86 percent of all women registering. Others report rates between 1 and 2 percent (Abell & Beischer, 1974; Chen, Palav, & Tricomi, 1972; Drury et al., 1970; Gyves, 1977). These traditional criteria, however, fall far short of the desired selectivity and specificity of a screening tool. Many investigators have found no significant relationship between any single criterion from the list of traditional screening factors and gestational diabetes. Only combinations of two or more criteria are associated with abnormal glucose tolerance and increased perinatal morbidity (Chen et al., 1972; Drury et al., 1970; Granat et al., 1979; O'Sullivan, Charles, Mahan, & Dandrow, 1973). In addition, investigators often must redefine a particular factor in a more limited way in order to report a meaningful association with gestational diabetes. For example, Soler and Malins (1971) limited "family history" to first degree relatives, and Granat et al. (1979) only found the history significant if the family member was a maternal sibling. The factor "glycosuria" is acknowledged to be the poorest of all the predictors. Drury et al. (1970) founds its specificity for glucose intolerance during pregnancy to be only 14.8 percent. Notelovitz (1970) reported the slightly higher figure of 18.4 percent but added that no fewer than 35 percent of known diabetics had no glycosuria.

Two other factors which are sometimes claimed to be associated with gestational diabetes are increased parity and maternal age. One study was found which supported increased parity as an independent predictor of gestational diabetes (Chen et al., 1972); most researchers found no such association after correcting for maternal age (Granat et al., 1979; O'Sullivan et al., 1973).

In a five year study by O'Sullivan et al. (1973), the following were obtained from two groups of prenatal patients:

A. A full clinical history which ascertained: 1) birth of a baby weighing nine pounds or more; 2) a history, in two or more pregnancies, of fetal death, neonatal death, congenital anomaly, prematurity, excessive weight gain, hypertension, or proteinuria; 3) a family history of diabetes, and 4) the mother's age.
B. A one-hour screening blood sugar test following a 50 gm glucose challenge.

Only known diabetics are excluded from this study. In the first group of 18,812 patients, only those women whose blood sugar level at one-hour was equal to or greater than 130 mg per 100 ml of whole blood were scheduled for a three-hour OGTT. In the second group of 986 women, all patients were offered a three-hour OGTT and 76 percent responded. The one-hour screening blood sugar tests were not significantly different between respondents and nonrespondents. The diagnosis of gestational diabetes was made from the three-hour OGTT using the previously discussed criteria (O'Sullivan, 1970). The sensitivity and specificity ratings were obtained and the screening blood sugar test and the more traditional screening factors were compared. The percentage of gestational diabetic patients correctly identified by the screening blood sugar test was 79 (sensitivity rate) compared to 63 percent for the traditional screening factors. The percent of patients who were correctly excluded by the screening blood sugar test (specificity rate) was 87. The specificity rate for the traditional screening factors was 56 percent. For the subpopulation of those patients 25 years or older, the sensitivity rating

of the blood sugar test was 88 percent and the specificity was 82 percent. The sensitivity and specificity of the traditional test for this older subgroup were 69 percent and 35 percent respectively.

Although they did not present the supporting data, O'Sullivan et al. (1973) claimed that maternal age is also an important screening factor for determining the presence of gestational diabetes. They considered older patients as those 25 years or older. This claim is supported by the findings of others (Granat et al., 1979; Pehrson, 1974; Spellacy et al., 1977). but in these studies the age group at higher risk for carbohydrate intolerance was 30 years and older. On the other hand, in three recent studies no relationship between maternal age and any untoward outcome of pregnancy was found (Adashi et al., 1979; Gabbe, Mestman, Freeman, Anderson, & Lowensohn, 1977; Gyves et al., 1977). However, in these studies a strict medical regime to maintain euglycemia throughout the pregnancy was maintained and may account for the favorable outcomes for all age groups. Adashi et al. (1979) also found a higher incidence of infants which were large for gestational age among mothers over 25 years old.

The recommendation of O'Sullivan et al. (1973) that a one-hour blood sugar test be used to screen for gestational diabetes was applied in a study by Amankwah et al. (1977). They administered a one-hour screening plasma glucose test after a 50 gm oral glucose load to 1,184 prenatal patients between 32 and 33 weeks gestation. All known diabetics were excluded. Of the 1,184 patients, 299 (25.3%) had positive screening tests and these received the

standard glucose tolerance test. Of these 299 patients, 71 (6%) were diagnosed as gestational diabetics. These investigators also pointed out that 57.6% were 25 years or older, 26.8% were obese, and 47.9% had a family history of diabetes. Sensitivity and specificity rates could not be computed since both a one-hour screening test as well as a three-hour OGTT had not been done on every patient. However, the authors did state that the glucose screening had markedly improved their yield of gestational diabetics and because of early, rigorous medical treatment, resulted in a marked improvement in pregnancy outcome.

Statement of the Problem

Since 1978 all prenatal patients of the Family Health Program of Utah are routinely given a one-hour glucose screening test for decreased glucose tolerance. All those with positive screening tests are then given a three-hour oral glucose tolerance test to rule out the diagnosis of gestational diabetes. The purpose of this retrospective study is to compare the number of gestational diabetics identified by a positive one-hour screening test to the number that would have been identified had this screening test been limited to those patients with the following traditional factors present.

1. Family history of diabetes;
2. previous large infant (weighing 9 lbs/4,000 g or more);
3. previous unexplained stillborn, neonatal death, prenature birth;
4. previous pregnancy complicated by hypertension (systolic $\geq$ 140

and/or diastolic $\geq$ 90 at rest on two or more occasions), proteinuria (2+ on two or more occasions), excessive weight gain (greater than 30 pounds for pregnancy), polyhydramnios or preeclampsia (as diagnosed by physician or CNM in the record).

Significance of This Study with Specific Reference to Nurse-Midwifery

Detection of gestational diabetes is the first step in providing early medical and nursing interventions which will improve the outcome of this high-risk pregnancy. Any research which could lead to an improvement in the screening process for this disease is thus of obvious medical worth and is of critical importance to the practice of nurse-midwifery.

The results of this type of research can also contribute to the trend toward a more holistic approach in health care delivery. Until recently, the focus of medicine and, to a somewhat lesser extent, nursing has been on pathology. "The span of holistic medicine is far broader, including prevention, life-style modification, psychological counseling, and supporting the patient as a responsible individual" (Pelletier, 1979, p. 38). The patient is invited to become an active participant and the primary source of positive change in his own health care. Such approaches are based on the principle that health is not the absence of disease. Rather, health care providers must both promote and maintain the optimal level of wellness possible for the whole person--body, soul, and mind--as well as treat and prevent disease (Bruhn, Cordova, Williams, & Fuentes, 1977; Fink, 1976).

Commitment to holistic patient care is embedded in the practice of American nurse-midwifery, as the written philosophy, functions, and standards of the American College of Nursing demonstrate. The midwife is mandated to work toward a colloquial relationship with both her patient and other health care workers. As long as the mother and newborn remain essentially healthy, a midwife is responsible for their management and complete care. However, of equal importance is the responsibility to be able to identify any deviations from the norm which would require immediate collaboration with a physician. Thus, research which aims to improve the identification of the high risk pregnant patient is especially helpful in improving this significant area of nurse-midwifery practice.

CHAPTER II

METHODS

Study Site, Population, and Data Collection

The Family Health Program of Utah (FHP), a branch of the Family Health Program of Southern California, is a staff model health maintenance organization which has two centers serving the greater Salt Lake City area. This nonhospital based, nonprofit corporation serves a broad spectrum of socioeconomic groups, although the typical patient is both middle-class and caucasian. The data for this study were gathered by reviewing the prenatal records of all women who both received their prenatal care and delivered their babies within the FHP health care system between May 1979 and April 1980. These women were identified by examining the delivery lists of the two FHP centers. When an infant's birthweight was not in the mother's chart the appropriate newborn pediatric record or hospital nursery record was also reviewed.

In these clinics all prenatal patients were routinely to be given a one-hour plasma glucose screening test at approximately 26 to 30 weeks gestation. Those with a positive one-hour screening test are then scheduled for a standard three-hour oral glucose tolerance test (OGTT). Patients were instructed to

consume a high carbohydrate diet for the three days just prior to either of these tests and to fast from midnight the night before (See Appendix). Assays of plasma glucose were performed by the glucose hexokinase method using an Abbot VP Chemistry Analyzer (See Appendix). Only women known to be diabetics prior to their pregnancy were intentionally excluded from this study.

Data Collected and Definition of Terms

Positive One-hour Screening Test

All women whose plasma glucose levels were 130 mg./100 ml. or greater one hour after a 50 g. oral glucose load were considered to have a positive one-hour screening test.

Positive Three-hour Oral Glucose Tolerance Test

Gestational diabetes was diagnosed when the result of a three-hour OGTT was positive. The test was considered positive if two or more of the following glucose levels were met or exceeded:

Fasting value	104 mg./100 ml.
One-hour value	190 mg./100 ml.
Two-hour value	167 mg./100 ml.
Three-hour value	138 mg./100 ml.

Traditional Screening Factors

Family history of diabetes. It was determined from the patient's chart whether any family members suffer from diabetes mellitus. The number in

each of the following categories was recorded: Parents, Siblings, Grandparents, Other Relatives.

Previous large infant. The number of previous babies whose birthweight equalled or exceeded 4000 grams (c. 9 lbs.) was recorded.

Poor obstetrical outcome. The reported numbers of previous spontaneous abortions, stillborn, neonatal deaths, and premature births were recorded.

Previous pregnancy complications. The number of previous pregnancies that were complicated by the following problems was recorded.

1. Hypertension: systolic $\geq$ 140 and/or diastolic $\geq$ 90 at rest on two or more occasions.
2. Proteinuria: 2+ on two or more occasions.
3. Polyhydramnios: as diagnosed by physician or C.N.M. in the record.
4. Preeclampsia: as diagnosed by physician or C.N.M. in the record.

Current Pregnancy Complications

It was noted whether the current pregnancy was complicated by any of the problems discussed above.

Additional Data

The following data were also collected by reviewing the patient's chart: maternal age, gravidity, prepregnancy weight, weight at time of delivery, height,

weight, and age (in weeks of gestation) of the infant at birth. The weight gained during pregnancy was computed from prepregnant weight and weight at time of delivery.

Analysis

The study population was categorized into subgroups for various parts of the analysis. These subgroups are: multigravous and primigravous women; those given and those not given one-hour screening tests; those with positive and those with negative one-hour tests; and gestational diabetic and nondiabetic mothers.

Continuous variables, such as birth weight and one-hour values of the screening test, were summarized by calculating means and standard deviations. Differences in means between the various subgroups were tested for statistical significance using t-tests.

Histories of diabetes in the family, previous large infant, poor obstetrical outcome, past pregnancy complications, and current pregnancy complications were treated as simply present or absent for the analysis. These and other discrete variables, such as parity, were summarized by computing frequency distributions. In order to determine whether there were any statistically significant associations between any of these variables or between these variables and those upon which the above subgroups are based, contingency tables were constructed and chi-square tests of independence were performed. Although percentages are generally reported for these attribute data, the chi-square tests were performed on the counts.

CHAPTER III

RESULTS

Description of the Study Population

The prenatal population for this study consisted of 630 patients. Twenty-nine percent of these women were primigravidas and 71 percent were multigravidas. The salient characteristics of these two subgroups and of the total population are presented in Table 1. The average woman in this study was about 25 years old and had had two or three babies previously. About 15 percent of the population was overweight at the beginning of their pregnancy. A large proportion (48%) gained more than 30 pounds during the course of their pregnancy. A larger proportion of the primigravidas gained excessive weight than did multigravidas ($X^2 = 4.10$; $\underline{df} = 1$; $\underline{p} < .05$). A significantly larger proportion of primigravidas also had pregnancy complications. This was entirely due to the higher incidence of preeclampsia among primigravidas (18.1% vis a vis 2.2% for multigravidas).

The mean birthweight of infants born to mothers in this study was 3417 grams. Infants of multigravidous women were significantly heavier than the infants of primigravidous women ($t = 2.34$; $\underline{df}$ 262; $\underline{p} < 0.05$). Others have also observed a direct relationship between infant birthweight and parity

Table 1

Characteristics of the Population of F.H.P. Clinic Patients
Who Delivered between May 1979 and April 1980

Variable	Primigravidas		Multigravidas		Total	
	n	$\bar{x}$ or %*	n	$\bar{x}$ or %	n	$\bar{x}$ or %
Maternal Age	182	21.4 (4.2)	448	26.2 (4.6)	630	24.8 (5.0)
Gravity	182	1	448	3.7	630	2.9
Overweight	173	11.5	438	16.5	612	15.1
Excess Weight Gain	180	65.7	438	45.0	618	48.4
Current Pregnancy Complications	182	11.0	448	2.2	630	14.6
Birthweight (g)	180	3340 (504)	441	3440 (504)	621	3417 (551)
Infant > 4000 g	180	10.0	441	12.9	621	12.1
Infant < 2500 g	180	3.3	441	5.0	621	4.5
Gestational Age	182	39.4 (2.8)	448	39.5 (1.9)	630	39.5 (2.2)
<38 weeks	182	11.5	448	8.3	628	8.9
>42 weeks	182	11.5	448	10.5	628	11.0
Traditional Screening Factors						
Family History of Diabetes	182	38.5	448	43.1	630	41.7
Previous Large Infant	182	--	448	13.8	630	10.0
Previous Poor Obstretical History	182	--	448	35.0	630	20.2
Previous Pregnancy Complications	182	--	448	10.5	630	7.3

*The mean (standard deviation) or the percent having an attribute are tabulated.

(Romney, Gray, Little, Merrill, Quilligan, & Stander, 1975, p. 86). There was no significant difference between multigravidas and primigravidas in the proportion bearing infants larger than 4000 grams nor in the proportion giving birth to infants less than 2500 grams.

There was no significant difference in the gestational age of infants born to multigravidas and primigravidas. The mean gestational age of infants in the population was 39.5 weeks.

Table 2 shows the distribution of patients with regard to the one-hour and three-hour glucose tolerance tests. One hundred women are missing from this portion of the study; 79 did not receive the one-hour screening test and 21 who had a positive screening test did not receive a three-hour OGTT. In order to check whether the women who did not receive a screening test were a nonrandom sample of the total population, they were compared to the subgroup who did receive the test. There were no significant differences between the two groups in age, gravidity, traditional screening factors, or current pregnancy problems. There was a significant difference in mean birthweight ($t = -2.0$; $df = 77.2$; $p < .05$) and in gestational age ($t = 3.2$; $df = 82$; $p < .005$). The infants of mothers who did not have the one-hour test averaged approximately 7 ounces lighter and were born about a week and a half earlier than those of mothers who had the test, although both means were within normal limits. There seems no reason to believe that the results based on the data from the subgroup who received a screening test cannot be generalized to the population as a whole. It should, however, be

Table 2

Distribution of Patients with Regard to One-hour Blood Sugar Screening Test and Three-hour OGTT

Patients with:	No 3° test	Negative 3° test	Positive 3° test
No One-hour test	78	1	0
Negative One-hour test	432	3	0
Positive One-hour test	21	88	7

noted that two previously diagnosed gestational diabetics did not receive screening tests.

In many cases one could not determine from the charts why patients did not receive a screening test. However, in nearly half the cases patients who did not receive the one-hour test had a history of noncompliance, repeated missed prenatal visits, and/or late registration for prenatal care. In the case of the 21 patients who had a positive screening test but no three-hour OGTT, 7 did not comply with the request for the test, 2 could not tolerate the glucose load, and for 11 there was no documented reason for missing the test. Four patients were given a three-hour OGTT despite a negative or missing one-hour test. Of these one had a very high, though not positive, blood sugar value and was bearing twins, two were very positive in terms of traditional screening factors, and one had a "defect in her pituitary gland." All four had negative three-hour OGTT's.

Fifty-nine percent of the study population were positive for one or more traditional screening factors. Since primigravidas have by definition no past obstetrical history, only a family history of diabetes, obesity, and possibly excessive weight gain are relevant traditional screening factors for them. There was no significant difference in the proportion of primigravidas and multigravidas who had a family history of diabetes. Of the traditional screening factors, a family history of diabetes was by far the most common for the whole population (42%), followed by poor obstetrical outcome (20%), history of previous large infant (10%), and poor obstetrical history (7%) (See Table 1). The distribution of the population relative to the traditional screening factors is shown in Table 3. Relatively few women were positive for more than two traditional screening factors.

Table 3

Proportion of the Study Population with Various Numbers of Traditional Screening Factors (TSF)

Variable	Primigravidas	Multigravidas	Total Group
Only one TSF	38.5%	44.2%	34.0%
One or more TSF*	38.5%	71.0%	59.4%
Two or more TSF*	--	26.8%	25.4%
Three or more TSF*	--	6.5%	7.2%
Four TSF	--	1.6%	1.2%

*This is a cummulative computation.

Effectiveness of the One-hour Glucose Screening Test

The main objective of this study was to compare the number of gestational diabetics identified by a positive one-hour screening test to the number identified by a positive one-hour screening test and by the presence of one or more traditional screening factors. Only those patients who received both a positive one-hour screening test and the three-hour OGTT could be used for this comparison. Ninety-five patients so qualified. A review of their medical histories indicated whether one or more of the traditional screening factors were positive. The results of this analysis are presented in Table 4. Two out of the seven identified gestational diabetics would have been missed by the traditional screening test.

Table 4

Number of Gestational Diabetics Identified by a One-hour Screening Test or by a Screening Test and Traditional Factors

	Negative Three-hour OGTT	Positive Three-hour OGTT
Positive One-hour Test	88	7
Positive One-hour Test and One or More TSF*	64	5
Positive One-hour Test and Two or More TSF*	24	4
Positive One-hour Test and Three or More TSF*	5	0
Positive One-hour Test and Four TSF	1	0

*This is a cummulative computation.

Comparison of Subgroups

Since the ultimate goal of this type of research is to find the best means of identifying a small, difficult to detect group of women who are transiently afflicted with a serious disease, comparisons were made between several subgroups within the study population. The purpose of these comparisons was to determine if any of the variables measured in this study were associated with a positive one-hour screening test or a positive three-hour OGTT.

Those with positive and those with negative one-hour screening tests were compared using the following variables: age, gravidity, obesity, excessive weight gain, current pregnancy complications, and traditional screening factors. No significant differences were found except for age; a larger proportion of patients 30 years old or older had positive one-hour tests than did younger patients ($X^2 = 8.43$; $\underline{df} = 2$; $\underline{p} < .05$) (See Table 5).

Similar comparisons were made between those with a positive and those with a negative three-hour OGTT. No significant differences were found (See Table 6).

Finally, the gestational diabetics were compared to the rest of the study populations (See Table 7). The only variable that differed significantly between the two populations was age. The mean age of the gestational diabetics was 28.7 years compared to 24.8 years for the rest of the study population ($t = 2.08$; $\underline{df} = 628$; $\underline{p} < 0.05$). The range for gestational diabetics

Table 5

Comparison of Study Variables between Patients with a Positive One-hour Screening Test and Patients with a Negative One-hour Screening Test

	Negative One-hour	Positive One-hour	X^2	df	p
Patient < 30 years old	371	64			
Patient ≥ 30 years old	85	31	8.43	1	<0.05
Primigravidas	164	36			
Multigravidas	271	80	1.48	1	ns
Not obese	370	94			
Obese	61	19	0.316	1	ns
No excessive weight gain	224	55			
Excessive weight gain	208	61	0.55	1	ns
No current pregnancy complications	370	98			
Current pregnancy complications	65	18	0.00	1	ns
No TSF	174	35			
≥ one TSF	261	81	3.35	1	ns

Table 6

Comparison of Study Variables between Patients with a Positive Three-hour OGTT and Patients with a Negative Three-hour OGTT

	Negative Three-hour	Positive Three-hour	X^2	df	p
Patient < 25 years old	48	0			
Patient ≥ 25 years old	44	7	5.155	1	<0.05
Primigravidas	32	1			
Multigravidas	60	6	0.48	1	ns
Not obese	75	4			
Obese	15	3	.23	1	ns
No excessive weight gain	42	2			
Excessive weight gain	50	5	.23	1	ns
No current pregnancy complications	42	2			
Current pregnancy complications	50	5	.63	1	ns
No TSF	29	2			
≥ one TSF	62	5	0.03	1	ns

Table 7

Comparison of Study Variables between Gestational Diabetics and Nondiabetic Prenatal Patients

	Gestational Diabetic	Nondiabetic Patients	X^2 or t	df	p
Mean Maternal Age	28.7	24.6	t = 2.08	628	<0.05
Primigravidas	1	224			
Multigravidas	6	399	X^2=0.63	1	ns
Not obese	4	520			
Obese	3	90	X^2=2.36	1	ns
No excessive weight gain	318	295			
Excessive weight gain	2	5	X^2=0.72	1	ns
No current pregnancy complications	7	531			
Current pregnancy complications	0	92	X^2=0.32	1	ns
No TSF	2	238			
≥ 1 TSF	5	385	X^2=0.02	1	ns
Infant < 4000 g	5	540			
Infant ≥ 4000 g	2	74	X^2=0.56	1	ns
Mean gestational age	39.5	39.5	t = .08	628	ns

was 25 to 37 years. Of the six gestational diabetic mothers who gave birth to a single baby, two had an infant that weighed more than 4000 grams. This is a larger proportion of large infants than in the general population; however, the chi-square test of independence was not significant. The sample size was quite small so one should probably be cautious about accepting the null hypothesis. What is statistically conservative is not necessarily clinically conservative. If large babies are associated with gestational diabetes, it is a cause for concern.

Macrosomia

No significant association was found between macrosomia and gravidity, current pregnancy complications, the results of a one-hour screening test, the result of a three-hour OGTT or with three of the four traditional screening factors (poor obstetrical outcome, pregnancy complications, and family history of diabetes) (See Table 8). A significant association was found between macrosomia and increased maternal age ($X^2 = 7.02$; $df = 2$, $p < .05$), obesity ($X^2 = 8.91$; $df = 1$; $p < .005$), excessive weight gain ($X^2 = 22.4$; $df = 1$; $p < .001$), a history of previous large infants ($X^2 = 22.7$; $df = 1$; $p < .001$). Of all babies born to mothers 25 years old or older 16.3 percent weighed more than 4000 grams. Only 9.3 percent of mothers younger than 25 years gave birth to large infants. About one out of every five infants born to mothers who gained more than 30 pounds during pregnancy weighed more than 4000 grams, whereas only one out of 16 infants born to mothers who

Table 8

Association between Macrosomia and Various Other Factors

Variable	No macrosomia	Macrosomia	X^2	df	p
Maternal age < 25 years	330	34			
Maternal age ≥ 25 years	215	42	6.24	1	<0.25
Primigravida	162	18			
Multigravida	383	58	0.91	1	ns
Obese	464	54			
Not obese	70	20	8.91	1	<0.03
No excessive weight gain	294	19			
Excessive weight gain	243	57	22.40	1	<0.01
No current pregnancy complications	470	59			
Current pregnancy complications	75	17	3.26	1	ns
Negative one-hour test	384	49			
Positive one-hour test	98	18	1.14	1	ns
Negative three-hour OGTT	76	16			
Positive three-hour OGTT	5	2	0.05	1	ns
Negative diabetic family history	319	46			
Positive diabetic family history	226	30	0.04	1	ns
Positive past obstet. outcome	233	42			
Negative past obstet. outcome	108	16	0.43	1	ns
No past pregnancy complica.	303	49			
Past pregnancy complications	38	8	0.17	1	ns
No past big baby	302	36			
Past big baby	39	21	22.68	1	<0.01

had no excessive weight gain were large. It is interesting that there was no association between excessive weight at the beginning of pregnancy and excessive weight during the pregnancy. The best predictor of macrosomia appears to be a history of previous large infants. Thirty-five percent of all women with a history of bearing one or more infants that weighed more than 4000 grams had another large baby. Only about 11 percent of the other multigravidas had a large baby.

CHAPTER IV

DISCUSSION AND CONCLUSIONS

Since all the patients in this study did not receive a three-hour OGTT, the true number of gestational diabetics in this population is not known. Thus, the sensitivity (the percent correctly identified; number discovered/ total number) and selectivity (percent correctly excluded; number excluded/ number true negatives) of neither the traditional screening test nor the one-hour glucose screening test can be determined. However, the fact that within the subpopulation that received a three-hour OGTT two more gestational diabetics were identified by the one-hour screening test than by the use of traditional screening factors suggests that the one-hour test is the more efficient screening tool. There is no reason to believe that this result is biased by a nonrandom selection of patients who received the screening test because the group who had a three-hour OGTT did not differ from the remainder of the population in any variables except gestational age and birthweight of their infants. The women who did not receive the screening test tended to deliver about a week and a half earlier and their babies were about 200 grams lighter. This probably reflects the fact that they received less prenatal care than did the other mothers and seems unlikely to be related to any tendency to develop gestational diabetes.

The results of this study support the assertion of O'Sullivan et al. (1973) that the age of the prenatal patient is an important factor in the identification of gestational diabetes. All seven of the identified gestational diabetics were 25 years old or older. O'Sullivan and his colleagues report that 84 percent of the gestational diabetics in their population was at least 25 years old.

A comparison of the distribution of traditional screening factors in this study and that of O'Sullivan et al. (1973) is presented in Table 9. A significantly higher proportion of the patients at the Family Health Program clinics had traditional screening factors present than did those in O'Sullivan's study ($X^2 = 58.26$; $df = 2$; $p = 0.001$). O'Sullivan's group found that 2.5 percent of their population was gestational diabetics. There was a 1.1 percent yield of gestational diabetics in this study. The difference in the proportion of identified gestational diabetics in the two studies is not significant ($X^2 = 0.22$; $df = 1$; $p < 0.05$), despite the fact that all the gestational diabetics were

Table 9

Comparison of the Distribution of Traditional Screening Factors in This Study Population and in the Population Studied by O'Sullivan et al. (1973)

	No TSF present	1 TSF present	2 TSF present
O'Sullivan's patients	10,534 (56%)	5,882 (31%)	2,446 (13%)
F.H.P. patients	256 (41%)	271 (43%)	103 (16%)

identified in their study (See Table 10). Amanhwak (1977) reported that 6 percent of his 1184 patients were identified as gestational diabetics. This is a surprisingly high figure since the United States national average for diabetes is only about 5 percent according to the most recent National Institutes of Health report (1978). One would expect a much lower incidence of the early, transient form of this disease. One explanation for their higher percentage is the unusually low cut-off blood sugar values they used for their three-hour OGTT. By definition the diagnosis of gestational diabetes is established when two or more predetermined blood sugar levels are met or exceeded resulting in a positive OGTT. The number of positive tests and consequently the number of identified gestational diabetics is therefore inversely proportional to the values set as the "cut-off" blood sugar levels. The three-hour cut-off values suggested by O'Sullivan and Mahan (1964) are well-accepted and are used when Somogyi-Nelson determinations are made using venous whole blood. When plasma rather than whole blood is used

Table 10

Comparison of the Diabetic and Nondiabetic Populations in the O'Sullivan et al. (1973) Study and the F. H. P. Centers

	Nongestational Diabetic	Gestational Diabetic
O'Sullivan's patients	917	19
F. H. P. patients	623	7

O'Sullivan and Kantor (1963) suggest increasing the three-hour values by 12 percent. Niejadlik, Dube, and Adamko (1973) suggest increasing these values by 13 percent. Amankwah (1977) used even a slightly smaller modification. The F.H.P. clinics use the blood sugar levels suggested by O'Sullivan and his colleagues and increase them by 15 percent, rounded to the nearest whole value, for plasma (except for an anomalously low three-hour value that was only increased by 10 percent). These various cut-off values are presented in Table 11. I was unable to discover the rational underlying the decision at F.H.P. to use the 15 percent modification. In the present instance, had the 13 or 14 percent modifications been used there would have been no change in the number of gestational diabetics identified. Had Amankwah's low cut-off values been used one more patient would have been identified as a bestational diabetic.

Table 11

Values Used as Cut-offs on the Three-hour OGTT

	O'Sullivan[a] (1964)	Amankwah[b] (1976)	13%[b]	14%[b]	15%[b]	F.H.P.[b]
Fasting	90	100 (11.1%)	101.7	102.6	103.5	104
One-hour	165	180 (9.1%)	186.5	188.1	189.8	190
Two-hour	145	160 (10.3%)	180.8	165.3	166.8	167
Three-hour	125	140 (12.0%)	141.3	142.5	143.8	138

[a]Values for whole blood.

[b]Values for blood plasma.

Estimation of the True Number of Gestational Diabetics

Out of 531 patients screened with a one-hour blood sugar test, 7 gestational diabetics were eventually identified. Another patient with a past history of gestational diabetes had a very positive one-hour screening test and an inconclusive three-hour OGTT. The three-hour test was aborted after a negative fasting level and a very high positive one-hour value had been determined because the patient began vomiting. This woman was not included among the diabetics although she was a likely candidate for inclusion. Therefore, there were 7 (and possibly 8) gestational diabetics (GD) identified in a population of 531 patients using a screening test which has an estimated sensitivity of 79 percent (O'Sullivan et al., 1973). Another two patients can be assumed to be present but undiagnosed. Nine to 10 true gestational diabetics in this group of 531 patients would extrapolate to 10 to 12 gestational diabetics for the 630 patients in the study population. Thus, if all 630 patients had received a three-hour OGTT, 10 to 12 patients would probably have been identified as diabetic. This would be an incidence of 1.6 to 1.9 percent compared to the 1.1 percent actually discovered in the population. If slightly lower values were used for the three-hour OGTT there would, of course, tend to be an increase in the incidence of identified gestational diabetes.

$$\frac{\text{7-8 GD}}{\text{531 patients}} \cong \text{79\% of all GD present} \therefore \frac{\text{9-10 GD}}{\text{531 patients}} \cong \text{100\% of GD present} \cong \frac{\text{10-12 GD}}{\text{630}}$$

HEALTH SCIENCES LIBRARY

Cost Analysis

At the Family Health Program of Utah a one-hour blood sugar screening test, according to the director of their laboratory, costs approximately $4.30 per test and a three-hour OGTT $7.30 per test. If all 630 patients in this study had received a three-hour OGTT and 10 to 12 gestational diabetics had been identified, the cost of identifying each diabetic would have been $460 to $383. If all 630 patients had received a one-hour screening test and the same proportion of positives occurred as was found in this study (22%), 139 patients would have required a three-hour OGTT. An estimated 9 to 10 gestational diabetics would have been identified. The cost per identified gestational diabetic in this case would be $415 to $374. Using a screening test the clinic saved $861 (23%), but identified an estimated 21 percent fewer diabetics than if the three-hour OGTT was routinely given (Table 12).

Though the cost of a procedure is often a major consideration in determining its use in any institution, it is generally not the only one. The advantages of giving every patient a three-hour OGTT is its 100% effectiveness in identifying all gestational diabetics within a given population and possibly its improved patient compliance, since they need only come for one rather than possibly two blood sugar tests. The advantage of using a one-hour screening test is that the majority of the patients will need to take a single shorter test. The overall laboratory costs will be less, though the cost per identified gestational diabetic may or may not be. Clearly each institution must weigh

Table 12

Comparison of Laboratory Costs Involved in Various Methods of Screening for Gestational Diabetes

Number of Total Patients	Number Patients One-hour	Cost One-hour Test	Number Patients Three-hour	Cost Three-hour Test	Total Cost	Number of Gestational Diabetics Identified	Cost per Gestational Diabetic Patient Identified
630[a]	--	--	630	$4599	$4599	10 - 12	$460 - $383
630[b]	630	$2709	139	$1029	$3738	9 - 10	$415 - $374
630[c]	531	$2283	100	$ 724	$3007	7	$429
630[d]	630	$2709	630	$4599	$7308	10 - 12	$731 - $609

[a]Line 1: Cost of giving all patients in this study a three-hour OGTT.

[b]Line 2: Estimated cost to screen with a one-hour blood sugar test in this study if patient compliance had been 100%.

[c]Line 3: Actual laboratory cost for use of one-hour glucose screening in this study.

[d]Line 4: Estimated laboratory cost for proposed research project to determine efficacy of one-hour screening test in which all patients would receive both a one-hour screening test and a three-hour OGTT.

these factors against their own resources, goals and the needs and characteristics of their particular patient populations in deciding what method to use to identify gestational diabetes.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

The main purpose of this study was to determine whether a one-hour blood sugar screening test is a more effective screening tool for identifying gestational diabetics than a test based on traditional screening factors. Of those patients who had a positive one-hour screening test two more gestational diabetics were identified by the one-hour screening test than by a test based on traditional factors.

Maternal age was also found to be an important factor in the identification of gestational diabetes. All seven identified gestational diabetics were 25 years old or older.

It is often thought that macrosomia is more likely among infants of gestational diabetics, and this is one of the reasons why practitioners try to identify the disease. In this study two of the six singleton births to gestational diabetics were infants larger than 4000 grams. However, this was not a significantly larger proportion of large infants than found in the population as a whole. A significant association was found to exist between macrosomia and maternal obesity, a weight gain of 30 or more pounds during pregnancy, and a maternal age of 25 years or more.

As a result of its retrospective design there were several problems

and limitations in this study. Patients could not be randomly assigned to experimental groups. Rather, in large part the patients themselves decided whether they did or did not have a one-hour or three-hour OGTT. Because only positive one-hour patients generally received a three-hour OGTT, the hypothesis that the one-hour screening test does indeed increase the yield of identified gestational diabetics could only be tested using a subpopulation and the true incidence of gestational diabetes within this patient population could only be estimated. The selectivity and sensitivity of the one-hour screening test could not be determined. Since the collection of data was limited to a chart review the problems of biased charting and incomplete records were present. Due to time limitation information regarding the infant was essentially limited to birthweight and gestational age. Many interesting questions regarding the outcome of the current pregnancy could not be asked.

The results of this study suggest several recommendations for further study. A prospective study of one to two years duration could be initiated in which all F. H. P. patients received both a one-hour screening test and a three-hour OGTT. The additional lab work would cost about $3,570 (Table 12). An alternative would be to have all patients of a predetermined random subsample of an appropriate sample size receive both tests. In addition to the information collected in the present study more detailed information should be obtained regarding infant outcome, such as morbidity/mortality rates, presence or absence of congenital abnormalities, appgar scores and dextrostick determinations. The results of the proposed study would provide a

definitive determination of the effectiveness of the various screening tests for gestational diabetes and of the true incidence of this disease within the clinic's population. Also, by obtaining information regarding maternal and infant outcome one could compare the results of treatment with those reported in the literature, and one would have a baseline against which to judge any changes in treatment that may be instituted in the future.

APPENDIX

Glucose Tolerance Test Diet

(150 grams carbohydrate)

1. Instructions:

   A. Follow this diet for three days prior to day of test.

   B. On morning of test, do not eat or drink after midnight (except water) until test is completed.

   C. The purpose of the diet is to consume 150 grams of carbohydrates per day. In order to accomplish this, the diet requires an increased intake of starchy foods, sugar and sweets. Eat or drink at least what the diet calls for. More food or liquids may be consumed.

   D. If certain foods or beverages listed on the diet are disliked, substitutions may be made by using the substitution list. Be sure, however, that the foods exchanged have the same carbohydrate value as the foods or beverages that are substituted.

2. Diet:

Breakfast	Carbohydrate Grams
1 glass (4 ounces) orange juice*	10
Eggs and meats, as desired	--
1 slice toast*	15
1 bowl cereal*	15
Butter or margarine, as desired	--
4 ounces milk (whole or skim)*	6
Coffee, tea as desired	--
2 teaspoons sugar (or 2 packages)*	10
	56

Lunch	
1 Sandwich (2 slices bread*) or 1 Hamburger on bun*	30
1 glass (8 ounces) milk (whole or skim)*	12
1 serving fresh fruit*	10
	52

*Type of food which must be eaten.

Dinner	Carbohydrate Grams
Meat or fish, as desired	--
1 serving (1/2 c) potatoes, rice or noodles*	15
1 slice bread*	15
Vegetables, as desired	--
Salad and dressing, as desired	--
1 serving fruit flavored gelatin*	15
Coffee, tea as desired	--
	45

Substitution List:

Beverages	
Chocolate milk, 1 glass (8 ounces)	25
Carbonated beverages, 1 can (12 ounces non-dietary)	40
Fruit juice, 1 glass (4 ounces) (except vegetable or tomato juice)	10
Breakfast Foods	
Doughnut or muffin, 1 each	15
French toast or pancake, 1 each	15
Syrup, 1 tablespoon	15
Dinner Foods	
Hot roll, 1 each	15
Cornbread, 1 square	15
Dried beans or peas, cooked, 1/2 cup	20
Corn on the cob, 1 each	20
Corn, kernels, 1/2 cup	15
Hot dog bun, 1 each	15
Hamburger bun, 1 each	30
Pizza, 1/8 of large pizza	25
Desserts	
Cake, 1 serving	15
Pudding, 1/2 cup	35
Sherbet, 1/2 cup	30
Brownie, 1 each	15
Banana, 1 medium	25
Miscellaneous	
Popcorn, 1 cup	10
Chocolate candy, 1 ounce	15
Hard candy, 1 ounce	20

SPINCHEM
REAGENT FOR THE DETERMINATION OF GLUCOSE

Product No. 86247, 89017, and 89019

A. Product Uses

'Spin Chem' Glucose Reagent is an enzymatic end point procedure for the in vitro quantitative assay of glucose. It is easily performed manually within 5 minutes, and has been adapted to many automated analyzers. Specific instrument instructions are available from SmithKline.

B. Test Summary

Elevated serum glucose levels (hyperglycemia) occur with diabetes, infection, hyperthyroidism, or uremia. Depressed glucose levels (hypoglycemia) are associated with over-administration of insulin or other antidiabetic medication, or diseases of the pituitary or adrenal glands. Searcy[1] gives an exhaustive list of factors, both physiological and pathological, which may alter circulating glucose levels.

Elevated urine glucose levels are associated with many of the states which produce hyperglycemia, while depressed urine glucose levels indicate urinary tract infection. CSF glucose levels are generally 70% of serum glucose levels. In bacterial infections of the CNS, however, CSF glucose levels may be significantly depressed.

The 'SPIN CHEM' Glucose Reagent is formulated to determine glucose in body fluids by a modification of the Barthelmai and Czok[2] procedure which employs HK and G-6-PD.

SmithKline has made modifications which speed completion of the reaction and eliminate the need for deproteinization of the sample. Substitution of NAD for NADP reduces reagent cost.

Abbreviations: ADP (adenoisine diphosphate); ATP (adenosine triphosphate); CNS (central nervous system); CSF (cerebrospinal fluid); G-6-P (glucose-6-phosphate); G-6-PD (G-6-P dehydrogenase); HK (hexokinase); NAD (nicotinamide adenine dinocleotide); $NADH_2$ (NAD, reduced); NADP (NAD phosphate); U/L (International Enzyme Unit).

C. Test Principles

$$\text{glucose} + \text{ATP} \longrightarrow \text{G-6-P} + \text{ADP}$$

$$\text{G-6-P} + \text{NAD} \longrightarrow \text{6-phosphogluconate} + NADH_2$$

The reaction is initiated by the addition of patient sample to the reagent. Although hexokinase reacts slightly with other hexose sugars, the assay is specific for glucose due to the high specificity of G-6-PD for G-6-P. Specificity is such that fructose, galactose, and mannose give activity less than 1% of that induced by an equivalent quantity of glucose.

An increase in absorbance at 334, 340, or 365 nm due to the formation of $NADH_2$ is directly proportional to the glucose concentration of the sample.

D. Reagent Composition

Concentration of reagent in final reaction mixture: ATP:800 µM; NAD 830 µM; Mg^{2+}: 3 mM; KH (yeast): 700 U/L; G-6-PD (microbial): 1100 U/L. Buffer pH 7.5 ± 0.1): Piperazine-N, N^1-bis (2-ethanesulfonic acid): 50 mM; sodium carbonate: 30 mM.

In addition to the ingredients specifically listed, the reagent contains a filler, a binder, and enzyme stabilizers.

E. Precautions for Users

For in vitro diagnostic use. When used as directed, 'SPIN CHEM' Glucose Reagent presents no hazard to the user.

F. Reagent Preparation and Stability

Store unopened reagent at 2° to 8°C; protect from light; do not freeze. Note expiration date stamped on product. Reagent stability cannot be guaranteed if transferred from the original container. Reconstitute each vial with 50 ml (Product No. 86247), 20 ml (Product No. 89017), or 6.5 ml (Product 89019) of distilled or deionized water, unless stated differently in a specific instrument application. If solution becomes turbid it must be discarded. Reconstituted reagent is stable 96 hours at 2° to 8°C. or 24 hours at 20° to 25°C.

G. Sample

Unhemolyzed serum, plasma, urine, or CSF. Sample preservatives are not necessary. Urine or CSF may be analyzed without pretreatment. Urine samples should be approximately five times the volume of the usual serum sample and should be assayed with a sample blank. Protein-free filtrates and similar solutions may also be assayed if they do not contain material which inhibits the reagent enzymes. Store samples at 2° to 8°C.

H. Interfering Substances

Although anticoagulants and preservatives, such as fluoride, in commonly

used concentrations do not interfere with this assay, abnormally high levels may prolong the time necessary to complete the reaction. If heparin is used but is not completely dissolved in sample, reagent addition may cause precipitation (cloudiness). Standards which contain sulfhydryl binding agents as preservatives, such as thimerosal, inhibit the assay reactions. Since the reaction is not dependent on glucose oxidase, uric acid and ascorbic acid do not interfere. Young, et al[3] give a comprehensive list of drugs and other substances known to alter the circulating glucose levels.

The average sample blank for 112 hospital patient specimens was 4.3 mg/dl measured as glucose. If maximum accuracy is desired, or if serum is hemolyzed, icteric, or lipemic, a sample blank must be run. For most specimens this sample blank correction is not significant, and therefore not required.

I. Procedural Instructions

For the following manual assay procedure, suitable glassware, timer, and a UV spectrophotometer are required along with the 'SPIN CHEM' Glucose Reagent, aqueous glucose standards (50, 100, and 300 mg/dl), and control sera.

If sample is hemolyzed, icteric, or lipemic a sample blank will be necessary.

Assay

1. Wavelength: 340 nm. Temperature: within 20° to 37°C.
2. Mark cuvettes for sample(s), control(s), standard(s), and a sample blank (if used).
3. Pipet into each cuvette: reagent, 1.5 ml. (Substitute saline in any sample blank.)
4. Bring cuvettes to reaction temperature.
5. Record initial absorbance, A of each cuvette.
6. Add: serum or plasma, control serum, or standard, 10 µl.
7. After 5 minutes record the final absorbance, A_f.

If the difference between A_f and A_i is greater than 1.7 for a sample, dilute 1:10 with saline and repeat the assay.

See Section K for calculations.

J. Calibration and Quality Control

Valid results depend upon an accurately calibrated instrument. Consult the instrument operating manual.

Include standards in every run; glucose standards containing benzoic acid or sodium benzoate are suitable (see Section H). Assay standards to determine calculation factors. Establish a new calibration curve routinely. Standards with values in either mg/dl or millimoles/liter may be used.

TARGET™ Normal and Abnormal Control Sera (Product No. 83001 and 83201 respectively), which have been assayed in our laboratory, are recommended to routinely check the precision and accuracy of the assay system. Satisfactory performance limits are included with these products.

The capacity of the reagent is 750 mg/dl with the manual procedure given in Section I. Specific instrument instructions list other values.

K. Calculations

One mmole of $NADH_2$ is produced for each nmole of glucose present.

Sample concentration (mg/dl) = $\Delta A_{sample} \times F$

To calculate a factor (F) a standard must be run with this assay. Determine $\Delta A_{standard} = A_i$. Then F = standard (mg/dl or millimoles/liter) ÷ $A_{standard}$. If more than one standard is run, calculate the average F. Determine $\Delta A_{sample} = A_f - A_i$. If a sample blank was run, subtract ΔA_{blank} from ΔA_{sample}. If sample was diluted 1:10, multiply final value by 10. Millimoles/liter = 0.0556 x mg/dl.

Example calculation: Absorbance of standard (200 mg/dl): $A_i = 0.103$, $A_f = 0.563$, $\Delta A_{standard} = 0.460$. F = 200 mg/dl ÷ 0.460 = 435. Absorbance of sample blank: 0.018. A_f (sample minus blank) = 0.267 - 0.018 = 0.249. $\Delta A_{sample} = 0.249 - 0.090 = 0.159$. Sample concentration = 0.159 x 435 = 69 mg/dl.

L. Procedural Limitations

With the manual procedure in Section I, the response of the reagent is not linear for samples with a concentration greater than 750 mg/dl ($\Delta A = 1.7$ at 340 nm). Specific instrument instructions may list other values.

Results may not be valid if determined more than 30 minutes after the reaction has begun.

Young et al[3] list drugs and other substances which interfere with this test. Please refer to Section H for additional information on interfering substances.

M. Expected Values

The normal range was established from the serum of 112 donors screened for normality with an automated neocuproine method.[4] The values obtained showed a 2 S.D. spread of: 65-105 mg/dl or 3.61-5.83 mmoles/l (corrected for blank) and 69-109 mg/dl or 3.83-6.05 mmoles/l (blank omitted).

N. Performance

Precision: The following precision data resulted from repeated analysis using the procedure in Section I. Analysis of serum pools over a 10-day period: 99 $\pm$ 3.9 mg/dl (C.V. = 3.6%), n = 20 (2 assays per day). Sensitivity: The sensitivity of this assay is such that 0.23A = 100 mg/dl using the procedure described. Correlation: Results obtained with 'SPIN CHEM' Glucose Reagent in the assay of 98 samples showed a correlation coefficient (r) $\geq$ 0.97 when compared to results found by assaying the same samples with a ferro-ferricyanide method.[5]

O. References

1. Searcy, R. L., Diagnostic Biochemistry, McGraw Hill, New York, N.Y., 1969. 2. Barthelmai, W., and Czok, R., Klin. Wochenschr. 40, 585 (1962). 3. Young, D.S., Pestaner, L.C., and Gibberman, V., Clin. Chem. 21, No. 5 (1975). 4. Brown, M.E., Diabetes 10, 60 (1961). 5. Glucose: Technical Laboratory Method N-16, Technicon™ Instrument Laboratory, Ardsley, N.Y.

SmithKline Instruments, Inc.
880 West Maude Ave.
Sunnyvale, CA 94086

REFERENCES

Abell, D. A., & Beischer, N. A. Evaluation of the three-hour oral glucose tolerance test in detection of significant hyperglycemia and hypoglycemia in pregnancy. Diabetes, 1975, 24, 874-880.

Abell, D. A., & Beischer, N. A. Routine testing for gestational diabetes, pregnancy, hypoglycemia, and fetal growth retardation, and the result of treatment. Journal of Perinatal Medicine, 1974, 4, 197-212.

Adam, P. A. J. Control of glucose metabolism in the human fetus and newborn infant. Advances in Metabolic Disorders, 1971, 5, 183-187.

Adashi, E. Y., Pinto, H., & Tyson, J. E. Impact of maternal euglycemia on fetal outcome in diabetic pregnancy. American Journal of Obstetrics and Gynecology, 1979, 133, 262-274.

Alford, F. P., Martin, F. I. R., & Pearson, M. J. The significance and interpretation of mildly abnormal oral glucose tolerance. Diabetologia, 1971, 7, 173-180.

Amankwah, K. S., Prentice, R. L., & Fleury, F. J. The incidence of gestational diabetes. Obstetrics and Gynecology, 1977, 49, 497-498.

Baker, D. P., Hutchinson, J. R., & Vaughn, D. L. Comparison of standard oral and rapid intravenous glucose tolerance tests in pregnancy. Obstetrics and Gynecology, 1968, 31, 475-481.

Bates, G. W. Management of gestational diabetes. Postgraduate medicine, 1974, 55, 55-58.

Benjamin, F., & Casper, D. J. Comparative validity of oral and intravenous glucose tolerance tests in pregnancy. American Journal of Obstetrics and Gynecology, 1967, 97, 488-492.

Bruhn, J. G., Cordova, F. D., Williams, J. A., & Fuentes, R. G. The wellness process. Journal of Community Health, 1977, 2, 209-221.

Burt, R. L. Carbohydrate metabolism in pregnancy. Clinics of Obstetrics and Gynecology, 1960, 3, 310-325.

Carrington, E. R. The effect of maternal prediabetes. Clinics of Obstetrics and Gynecology, 1960, 3, 911-920.

Catt, K. J. Growth hormone. Lancet, 1970, 1, 933-939.

Chen, W., Palav, A., & Tricomi, V. Screening for diabetes in a prenatal clinic. Obstetrics and Gynecology, 1972, 40, 567-574.

Churchill, J. A., Brendes, H. W., & Nemore, J. Neuropsychological deficits in children of diabetic mothers. American Journal of Obstetrics and Gynecology, 1969, 105, 257-268.

Coustan, D. R., & Lewis, S. B. Insulin therapy for gestational diabetes. Obstetrics and Gynecology, 1978, 51, 306-310.

Dandrow, R. V., & O'Sullivan, J. B. Obstetric hazard of gestational diabetes. American Journal of Obstetrics and Gynecology, 1966, 96, 1144-1147.

Drury, M. I. Latent diabetes in pregnancy. Journal of Obstetrics and Gynecology of the British Commonwealth, 1970, 77, 24-28.

Felig, P. Body fuel metabolism and diabetes mellitus in pregnancy. Medical Clinics of North America, 1977, 61, 43-66.

Fink, D.L. Holistic health: Implications for health planning. American Journal of Health Planning, 1976, 1, 23-31.

Frantz, A. G., & Rabkin, M. T. Effects of estrogen and sex difference on secretion of human growth hormone. Journal of Clinical Endocrinology and Metabolism, 1965, 25, 1470-1480.

Farquhar, J. W. Diabetes and the fetus: Questions which need answers. Canadian Medical Association Journal, 1971, 105, 289-292.

Freinkel, N. Aspects of the endocrine regulation of lipid metabolism. In Dawson, R. M. C., & Rhodes, D. N. (Eds.), Metabolism and physiological significance of lipids. London: John Wiley & Sons, Inc., 1964.

Gabbe, S. G., Mestman, J. H., Freeman, R. K., Anderson, G. V., & Lowensohn, R. I. Management and outcome of class A diabetes mellitus. American Journal of Obstetrics and Gynecology, 1977, 127, 465-469.

Garnet, J. D., Helsel, E. V., & Piver, M. S. One-hour intravenous glucose tolerance test: An accurate screening test for diabetes during pregnancy. Obstetrics and Gynecology, 1968, 32, 249-253.

Greenhill, J. P., & Friedman, E. A. Biological principles and modern practice of obstetrics. Philadelphia: W. B. Saunders Co., 1974.

Gyves, M. T., Rodman, H. M., Little, A. B., Fanaroff, A. A., & Merkatz, I. R. A modern approach to management of pregnant diabetics: A two-year analysis of perinatal outcomes. American Journal of Obstetrics and Gynecology, 1977, 128, 606-616.

Hadden, D. R., & Harley, J. M. G. Potential diabetics and the foetus. Journal of Obstetrics and Gynaecology of the British Commonwealth, 1967, 74, 669-674.

Hadden, D. R., Harley, J. M. G., Kajtar, T. J., & Montgomery, D. A. A prospective study of three tests of glucose tolerance in pregnant women selected for potential diabetes with reference to the foetal outcome. Diabetologia, 1971, 7, 87-93.

Hagbard, L., & Svanborg, A. Prognosis of diabetes with onset during pregnancy. Diabetes, 1960, 9, 296-302.

Haworth, J. C., & Dilling, L. A. Effect of abnormal glucose tolerance in pregnancy on infant mortality rate and morbidity. American Journal of Obstetrics and Gynecology, 1975, 122, 555-560.

Haworth, J. C., & Dilling, L. A. Relationship between maternal glucose intolerance and neonatal blood glucose. The Journal of Pediatrics, 1976, 89, 810-813.

Hohe, P. T. Glucose tolerance testing during pregnancy: Comparison of standard 3-hour glucose tolerance test with a single 2-hour glucose-load test. Obstetrics and Gynecology, 1971, 38, 693-696.

Jackson, W. P. U. Studies in pre-diabetes. British Medical Journal, 1952, 2, 690-696.

Javier, Z., Gershberg, H., & Hulse, M. Ovulatory suppressants, estrogens, and carbohydrate metabolism. Metabolism, 1968, 17, 443-456.

Karlsson, K., & Kjellmer, I. The outcome of diabetic pregnancies in relation to the mother's blood sugar level. American Journal of Obstetrics and Gynecology, 1972, 112, 213-220.

Khojandi, M., Tsai, A., Y/M, & Tyson, J. E. Gestational diabetes: The dilemma of delivery. Obstetrics and Gynecology, 1974, 43, 1-6.

Koller, O. Diabetes and pregnancy. Acta Obstetrica et Gynaecologia Scandinavica, 1953, 33, 80-84.

Lunnell, N.O. Intravenous glucose tolerance in women with previously complicated pregnancies. Acta Obstetrica et Gynaecologia Scandinavica, 1966, 45 (suppl. 4), 7-89.

MacAffee, C. J. J., & Beischer, N. A. The relative value of the standard indications for performing a glucose tolerance test in pregnancy. Medical Journal of Australia, 1974, 1, 911-914.

McKeown, T., & Gibson, J. R. Observations on all births (23,970) in Birmingham, 1947. British Journal of Social Medicine, 1951, 5, 259-264.

Mickal, A., Begneaud, W. P., & Weese, W. H. Glucose tolerance and excessively large infants: A twelve year follow-up study. American Journal of Obstetrics and Gynecology, 1966, 94, 62-64.

Moss, J. M., & Mulholland, H. B. Diabetes and pregnancy, with special reference to the prediabetic state. Annals of Internal Medicine, 1951, 34, 678-691.

National Institutes of Health. National Diabetes Advisory Board 2nd Annual Report. U. S. Dept. Health, Education, and Welfare, Public Health Service. NIH Publ. No. 79-1902, March, 1979.

Navarrete, V. N., Rojas, C. E., Alger, C. R., & Paniagua. Subsequent diabetes in mothers delivered of a malformed child. Lancet, 1970, 2, 993-994.

Niejadlik, D. C., Dube, A. H., & Adamko, S. M. Glucose measurements and clinical correlations. Journal of the American Medical Association, 1973, 224, 1734-1736.

Notelovitz, M. Diabetes screening during pregnancy. Diabetologia, 1970, 6, 141-147.

Ocampo, P. T., Coseriu, V. G., & Quilligan, E. J. Comparison of standard oral glucose tolerance test and rapid intravenous glucose tolerance test in normal pregnancy. Obstetrics and Gynecology, 1964, 24, 580-583.

O'Sullivan, J. B. Gestational diabetes, unsuspected, asymptomatic diabetes in pregnancy. The New England Journal of Medicine, 1961, 264, 1082-1085.

O'Sullivan, J. B. Gestational diabetes and its significance. Advances in Metabolic Disorders, 1970, 1 (Suppl.), 339-344.

O'Sullivan, J. B., Charles, D., Mahan, C. M., & Dandrow, R. V. Gestational diabetes and perinatal mortality rate. American Journal of Obstetrics and Gynecology, 1973, 16, 901-904.

O'Sullivan, J. B., Gellis, S. S., & Tenney, O. T. Gestational blood glucose levels in normal and potentially diabetic women related to the birth weight of their infants. Diabetes, 1966, 15, 466-470.

O'Sullivan, J. B., & Kantor, N. Variability of blood sugar levels with an automated method. Public Health Reports, 1963, 78, 1023-1029.

O'Sullivan, J. B., & Mahan, C. M. Criteria for the oral glucose tolerance test in pregnancy. Diabetes, 1964, 13, 278-285.

O'Sullivan, J. B., Mahan, C. M., Charles, D., & Dandrow, R. V. Screening criteria for high-risk gestational diabetic patients. American Journal of Obstetrics and Gynecology, 1973, 116, 895-900.

O'Sullivan, J. B., Mahan, C. M., Charles, D., & Dandrow, R. V. Medical treatment of the gestational diabetic. Obstetrics and Gynecology, 1974, 43, 817-821.

Paton, D. M. Pregnancy in the diabetic patient. American Journal of Obstetrics and Gynecology, 1948, 56, 558-560.

Pedersen, J., Molsted-Pedersen, L., & Anderson, B. Assessors of fetal perinatal mortality in diabetic pregnancy. Diabetes, 1974, 23, 302-305.

Pedowitz, P., & Shlevin, E. L. Perinatal mortality in the unsuspected diabetic. Obstetrics and Gynecology, 1957, 9, 524-531.

Pehrson, S. L. A study of the relationship between some prediabetic stigmas, glucose tolerance in late pregnancy, and the birthweight of the children. Acta Obstetrica et Gynaecologia Scandinavica, 1974, 33, 1-131.

Pelletier, K. R. Holistic medicine from stress to optimum health. New York: Delacorte Press/Seymour Lawrence, 1979.

Pildes, R. S. Infants of diabetic mothers. New England Journal of Medicine, 1973, 289, 902-904.

Posner, B. I. Insulin metabolizing enzyme activities in human placental tissue. Diabetes, 1973, 22, 552-563.

Reis, R. A., de Costa, E. J., & Allweiss, M. D. The management of the pregnant diabetic woman and her newborn infant. American Journal of Obstetrics and Gynecology, 1950, 60, 1023-1039.

Romney, S. L., Gray, M. J., Little, A. B., Merrill, J. A., Quilligan, E. J., & Stander, R. Gynecology and obstetrics: The health care of women. New York: McGraw-Hill Book Co., 1975.

Silverstone, F. A., Solomons, E., & Rubricius, J. The rapid intravenous glucose tolerance test in obstetrical patients with a family history of diabetes. Diabetes, 1963, 12, 398-405.

Singh, M. M., & Arshat, H. Comparison of oral and intravenous glucose tolerance tests in the diagnosis of diabetes in pregnancy. British Journal of Obstetrics and Gynaecology, 1978, 85, 536-540.

Soler, N. G., & Malins, J. M. Indications for oral glucose--tolerance tests during pregnancy. Lancet, 1971, 2, 724-726.

Spellacy, W. N., & Cohn, J. E. Human placental lactogen levels and daily insulin requirements in patients with diabetes mellitus complicating pregnancy. Obstetrics and Gynceology, 1973, 42, 330-333.

Spellacy, W. N., & Goetz, F. E. Plasma insulin in normal late pregnancy. New England Journal of Medicine, 1963, 268, 988-991.

Stallone, L. A., & Ziel, H. K. Management of gestational diabetes. American Journal of Obstetrics and Gynecology, 1974, 119, 1091-1094.

Stehbens, J. A., Baker, G. L., & Kitchell, M. Outcomes at ages 1, 3, and 5 years of children born to diabetic women. American Journal of Obstetrics and Gynecology, 1977, 127, 408-413.

Trayner, I. M., Wellborn, T. A., Rubenstein, A. M., & Fraser, T. R. Serum and urine insulin in late pregnancy and in a few pregnant latent diabetics. Journal of Endocrinology, 1967, 37, 443-453.

Tyson, J. E., & Hock, R. A. Gestational and pregestational diabetes: An approach to therapy. American Journal of Obstetrics and Gynecology, 1976, 125, 1009-1027.

Velasco, M. S. A., Benjamin, F., & Gordon, H. H. Glucose tolerance tests in pregnancy and clinical manifestations in the offspring. American Journal of Obstetrics and Gynecology, 1966, 96, 930-937.

Wilkerson, H. L. C. Diagnostic evaluation of oral glucose tolerance tests in nondiabetic subjects after various levels of carbohydrate intake. New England Journal of Medicine, 1960, 262, 1047-1053.

Wilkerson, H. L. C., & O'Sullivan, J. B. A study of glucose tolerance and screening criteria in 752 unselected pregnancies. Diabetes, 1963, 12, 313-318.

Williger, V. M. Fetal outcome in the diabetic pregnancy. American Journal of Obstetrics and Gynecology, 1966, 94, 57-61.

Yen, S. S. C., Tsai, C. C., & Vela, P. Gestational diabetogenesis: Quantitative analyses of glucose-insulin interrelationship between normal pregnancy and pregnancy with gestational diabetes. American Journal of Obstetrics and Gynecology, 1971, 111, 792-800.